(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 178 034 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
06.02.2002 Bulletin 2002/06

(21) Application number: **01306484.5**

(22) Date of filing: **27.07.2001**

(51) Int Cl.[7]: **C07C 233/83**, C07C 271/22, A61K 31/195, A61P 25/00, A61P 25/08

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **01.08.2000 GB 0018828**

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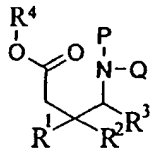
(54) Alkyl amino acid derivatives useful as pharmaceutical agents

(57) GABA-related pro-drugs of the formula (III) are provided that when administered to humans or other mammals provide an increased duration of active compound in the plasma compared to compounds of corresponding structure in which labile groups are not present. The compounds are of the formula (III)



(III)

In the above formula:

P represents hydrogen or methyl;
Q represents a labile amine- or amide-forming organic group that becomes removed in the human or animal body;

R^1 represents straight or branched C_2 - C_6 alkyl, C_3 - C_6 cycloalkyl or phenyl;
R^2 represents hydrogen or methyl; and
R^3 represents hydrogen, methyl or carboxyl; and
R^4 represents hydrogen or a labile ester-forming group selected from substituted and unsubstituted C_1 - C_6 alkyl, benzyl and phenyl groups that become removed in the human or animal body. In the above formula when R^1 is phenyl, R^2, R^3 and R^4 are not simultaneously hydrogen. Pharmaceutically acceptable salts of any salt-forming compound within the above class are also included. The compounds may be used to treat a range of neurological conditions, e.g. epilepsy and pain.

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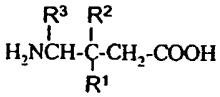
Description

FIELD OF THE INVENTION

[0001] This invention relates to novel alkyl amino acid derivatives useful as pharmaceutical agents, to processes for their production, to pharmaceutical compositions containing them, and to their use for the treatment of the neurological conditions set out below.

BACKGROUND TO THE INVENTION

[0002] US-A-5563175 describes compounds of the formula (I)

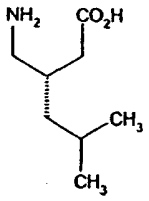


(I)

in which:

R^1 represents straight or branched C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or phenyl;
R^2 represents hydrogen or methyl; and
R^3 represents hydrogen, methyl or carboxyl.

[0003] The compounds (including their pharmaceutically acceptable salts) are structural analogues of γ-aminobutyric acid (GABA) and were stated to activate L-glutamic acid decarboxylase (GAD), to bind to a novel binding site, to be useful in anti-seizure therapy for central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive diskinesia and spasticity, and also to exhibit antidepressant, anxiolytic and antipsychotic activity. The most preferred compounds were those where R^3 and R^2 were hydrogen and R^1 was isobutyl, the (S)-(+) enantiomer of formula (II) being the most preferred.



(II)

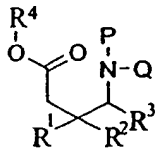
[0004] That compound is variously called 4-amino-3-(2-methylpropyl)butanoic acid, 3-(aminomethyl)-5-methylhexanoic acid, β-isobutyl-γ-aminobutyric acid, isobutyl-GABA, isobutylgaba and pregabalin.

[0005] US-A-6001876 discloses that the above compounds are useful in pain therapy. US-A-5840956 discloses methods for making (±)-isobutylgaba and for obtaining from it (S)-isobutylgaba. The disclosures of all the above patents are hereby incorporated by reference.

SUMMARY OF THE INVENTION

[0006] A problem with which this invention is concerned is the production of compounds useful in the manner of pregabalin, especially in pain therapy, that when administered to humans or other animals provide an increased duration of active ingredient in the plasma.

[0007] That problem is unexpectedly solved, according to the invention, by pro-drugs of pregabalin the compounds of the formula (III)



(III)

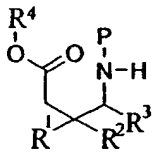
in which:

P is hydrogen or methyl;
Q is a labile amine- or amide-forming organic group that becomes removed in the human or animal body;
R^1 is straight or branched C_2 - C_6 alkyl, C_3 - C_6 cycloalkyl or phenyl;
R^2 is hydrogen or methyl; and
R^3 is hydrogen, methyl or carboxyl; and
R^4 is hydrogen or a labile ester-forming group selected from substituted and unsubstituted C_1 - C_6 alkyl, benzyl and phenyl groups that become removed in the human or animal body, and
a pharmaceutically acceptable salt of any salt-forming compound within the above class,
but excluding compounds in which R_1 is phenyl and R^2, R^3 and R^4 are each hydrogen.

[0008] It is believed that a pro-drug of the above formula when administered to a human or other animal, especially a mammal, enters the bloodstream by passive diffusion along the whole length of the intestine, which gives a much longer duration of effectiveness. The pro-drug may not itself be biologically active, but decomposes to the corresponding active compound in plasma.

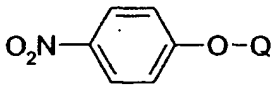
[0009] Certain of the compounds of the invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are biologically equivalent to unsolvated forms and are encompassed within the scope of the invention. Certain of the compounds of the invention possess one or more chiral centers and each center may exist in the R or S configuration. The invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof. It also includes salts of any of the above compounds with physiologically acceptable cations or anions.

[0010] The invention also provides a method for making a compound of the formula (III) above, which comprises:
coupling a compound of the formula:



(V)

in which P and R^1 - R^4 have the meanings given above and in which said compound is in the form of a free base or an ammonium salt with a compound of the formula (VI)



(VI)

or QCl, where (in each case) Q has the meaning given above;
and the invention also provides a method for making a compound of the formula (III) above, which comprises coupling a compound of the formula (V) that is a carboxylic acid, optionally employing the further step of esterifying the carboxyl group with a substituted or unsubstituted C_1 - C_6 alkanol, benzyl alcohol or phenol.

[0011] The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (III) above and a pharmaceutically acceptable carrier.

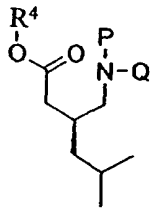
[0012] In a further aspect the invention provides the use of a compound of formula (III) in the manufacture of a medicament for the treatment of any of the following:

epilepsy; hypokinesia; a neurodegenerative disorder; anxiety; pain;	a faintness attack; a cranial disorder; depression; panic; a neuropathological disorder; a digestive disorder.

[0013] In a further aspect, the invention provides a method for treating any of the above disorders which comprises administering a therapeutically effective amount of a compound of formula (III) to a human or animal in need of said treatment.

DESCRIPTION OF PREFERRED FEATURES

[0014] One class of pro-drugs of the invention, which is preferred on account of the relatively high activity of the parent compound, comprises isobutylgaba pro-drugs of the formula (IV)

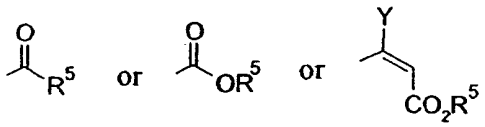


(IV)

in which P, Q and R^4 have the meanings given above, and pharmaceutically acceptable salts of any salt-forming compound within the above class.

[0015] Where R^4 is not hydrogen, it is desirable that it should be more labile than Q so that under physiological conditions the free acid forms first and unwanted reactions between the amino and carboxyl groups are avoided. Suitable values of R^4 other than hydrogen are ethyl, *iso*-propyl, benzyl, phenyl, methyl and t-butyl.

[0016] The group Q may be one which can be removed hydrolytically under physiological conditions, in which case it may be

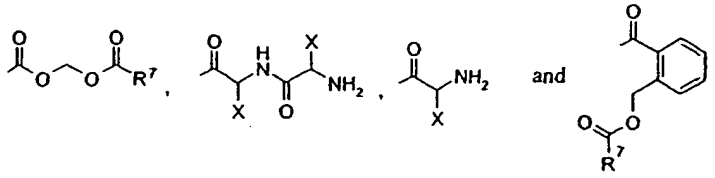


in which:

R^5 is hydrogen, straight or branched chain C_1 - C_6 alkyl, phenyl or benzyl in which the benzene ring may be substituted or unsubstituted; and

Y is hydrogen, straight or branched chain C_1 - C_6 alkyl, or $-CH_2CO_2R^6$ in which R^6 represents straight or branched chain C_1 - C_6 alkyl

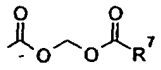
[0017] Alternatively, the group Q may be one which can be removed enzymatically under physiological conditions, in which case it may be selected from



in which:

R^7 is hydrogen, straight or branched chain, phenyl or benzyl in which either or each benzene ring may be substituted or unsubstituted; and
X represents a phenyl group or any of the side chains of the 20 naturally encoded α-amino acids.

[0018] In a preferred group of compounds Q is



wherein R^7 is C_1 - C_6 alkyl (preferably methyl or t-butyl) or phenyl.

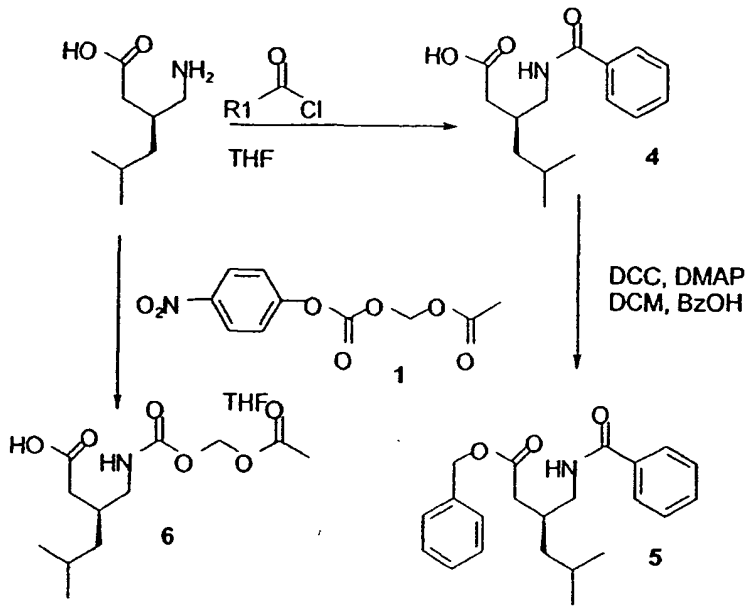
[0019] Compounds according to the invention include *inter alia*:

(S)-3-(Benzoylaminomethyl)-5-methylhexanoic acid;
(S)-Benzyl 3-(acylaminomethyl)-5-methylhexanoate;
(S)-3-[*N*-(acetoxymethyleneoxycarbonyl)aminomethyl]-5-methylhexanoic acid;
(S)-3-[*N*-((2,2-dimethylpropionyloxy)methyleneoxycarbonyl)-aminomethyl]-5-methylhexanoic acid;
(S)-3-[*N*-(benzoyloxymethyleneoxycarbonyl)aminomethyl]-5-methylhexanoicacid; and
pharmaceutically acceptable salts of any of the above.

[0020] Various methods may be used to prepare compounds according to the invention e.g. from starting materials disclosed in the patents referred to above.

[0021] For example, amide prodrugs of pregabalin may be prepared by reacting pregabalin with an acid chloride in an ether e.g. tetrahydrofuran at ambient temperatures. A carboxylic acid group of the resulting prodrug may be converted to an ester group by reaction with an alcohol e.g. by reaction with benzyl alcohol in the presence of 1,3-dicyclohexyldiimide (DCC) and 4-dimethylaminopyridine (DMAP) in a halogenated hydrocarbon solvent e.g. dichloromethane (DCM) at ambient temperatures. (Acyloxy)alkyl carbamate prodrugs of pregabalin may be prepared by reacting pregabalin with an acyloxyalkyl *p*-nitrophenyl carbonate in an ether e.g. tetrahydrofuran at ambient temperatures.

[0022] These reactions are illustrated in the following reaction scheme by reference to preferred reagents and preferred final products (4), (5) and (6), it being understood that a similar scheme applies *mutatis mutandis* to the use of other acyl chlorides, acyloxymethylene carbonates and optionally esterifying reagents, for the preparation of other final products of formula (III) above.



[0023] The compounds of the invention are expected to be useful in the treatment of epilepsy. They may also be used as mimetic agents for neurodegenerative disorders. Such neurodegenerative disorders are, for example, Alzheimer's disease, Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis. The present invention also covers treating acute brain injury. These include but are not limited to: stroke, head trauma, and asphyxia. Stroke refers to a cerebral vascular disease and may also be referred to as a cerebral vascular accident (CVA) and includes acute thromboembolic stroke. Stroke includes both focal and global ischemia. Also, included are transient cerebral ischemic attacks and other cerebral vascular problems accompanied by cerebral ischemia such as in a patient undergoing carotid endarterectomy specifically or other cerebrovascular or vascular surgical procedures in general, or diagnostic vascular procedures including cerebral angiography and the like. Other incidents are head trauma, spinal cord trauma, or injury from general anoxia, hypoxia, hypoglycemia, hypotension as well as similar injuries seen during procedures from embole, hyperfusion, and hypoxia. Treatment with the present compounds could also be useful in a range of incidents, for example, during cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest, and status epilepticus. A skilled physician will be able to determine the appropriate situation in which subjects are susceptible to or at risk of, for example, stroke as well as suffering from stroke for administration by methods of the present invention.

[0024] The compounds of the invention are also expected to be useful in the treatment of depression. Depression can be the result of organic disease, secondary to stress associated with personal loss, or idiopathic in origin. There is a strong tendency for familial occurrence of some forms of depression suggesting a mechanistic cause for at least some forms of depression. The diagnosis of depression is made primarily by quantification of alterations in patients' mood. These evaluations of mood are generally performed by a physician or quantified by a neuropsychologist using validated rating scales, such as the Hamilton Depression Rating Scale or the Brief Psychiatric Rating Scale. Numerous other scales have been developed to quantify and measure the degree of mood alterations in patients with depression, such as insomnia, difficulty with concentration, lack of energy, feelings of worthlessness, and guilt. The standards for diagnosis of depression as well as all psychiatric diagnoses are collected in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) referred to as the DSM-IV-R manual published by the American Psychiatric Association, 1994.

[0025] The present compounds are also expected to be useful in the treatment of anxiety and of panic as demonstrated by means of standard pharmacological procedures.

[0026] The compounds of the invention are also expected to be useful in the treatment of pain. Pain refers to acute as well as chronic pain. Acute pain is usually short-lived and is associated with hyperactivity of the sympathetic nervous system. Examples are postoperative pain and allodynia. Chronic pain is usually defined as pain persisting from 3 to 6 months and includes somatogenic pains and psychogenic pains. Other pain is nociceptive. Still other pain is caused by injury or inflammation of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis.

Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Neuropathic pain includes, but is not limited to pain caused by nerve injury such as, for example, the pain diabetics suffer from. Psychogenic pain is that which occurs without an organic origin such as low back pain, atypical facial pain, and chronic headache. Other types of pain are: inflammatory pain, osteoarthritic pain, trigeminal neuralgia, cancer pain, diabetic neuropathy, restless leg syndrome, acute herpetic and postherpetic neuralgia, causalgia, brachial plexus avulsion, occipital neuralgia, gout, phantom limb, burn, and other forms of neuralgia, neuropathic and idiopathic pain syndrome.

[0027] The present compounds are also expected to be useful in the treatment of digestive disorders such as visceral pain, pain associated with cancer, the irritable bowel syndrome, infection and inflammation.

[0028] The present compounds can be prepared and administered in a wide variety of oral and parenteral dosage forms. Oral dosage forms are preferred but parenteral dosage forms may also be used where it is desired to use the kinetics of decomposition into the corresponding active compound.

[0029] Thus, they can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, they can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component either a compound of the invention or a corresponding pharmaceutically acceptable salt.

[0030] For preparing pharmaceutical compositions from the present compounds, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0031] In powders, the carrier is a finely divided solid that is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0032] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted, and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0033] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol.

[0034] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents as desired.

[0035] Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0036] Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilising agents, and the like.

[0037] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0038] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1 g according to the particular application and the potency of the active component. In medical use the drug may be administered three times daily as, for example, capsules of 100 or 300 mg. The composition can, if desired, also contain other compatible therapeutic agents.

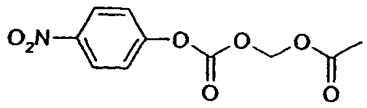
[0039] In therapeutic use, the compounds utilised in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular

situation is within the skill of the art. Generally, treatment is initiated with smaller dosages that are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage maybe divided and administered in portions during the day, if desired.

PREPARATION OF REAGENTS

Acetoxymethyl *p*-nitrophenyl carbonate (1)

[0040]



1

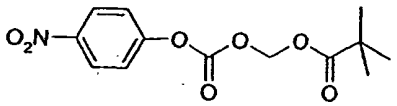
[0041] Carbonate 1 was prepared as described in *J.Med.Chem*, 1988, **31**, 318-322 (5.29 g, 98%). Its characteristics were described in *J.Org.Chem*, 1997, **62**, 1356-1362.

ν_{max}(film)/cm^{-1}1776 (C=O), 1526 (C=C, Ar).

δ_H(400 MHz; $CDCl_3$) 2.19 (3H, s, CH_3), 5.88 (2H, s, OCH_2O), 7.42 (2H, d, *J* 9.6, *p*-NO_2Ar*H*), 8.30 (2H, d, *J* 9.2, *p*-NO_2Ar*H*).

2,2-dimethylpropionyloxymethyl *p*-nitrophenyl carbonate (2)

[0042]



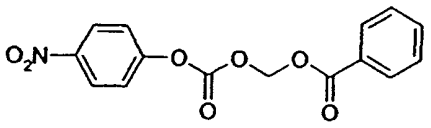
2

[0043] Carbonate **2** was also prepared as described in the above paper (1.16 g, 60%).

ν_{max}(film)/cm^{-1} 1779, 1759 (C=O), 1530 (C=C, Ar).
δ_H(400 MHz; $CDCl_3$) 1.26 (9H, s, ^{t}butyl), 5.89 (2H, s, OCH_2O), 7.41 (21 d, *J* 9.4, *p*-NO_2Ar*H*), 8.30 (2H, d, *J* 9.2, *p*-NO_2Ar*H*).

Benzoyloxymethyl *p*-nitrophenyl carbonate (3)

[0044]



3

Carbonate 3 was also prepared as described in the above paper (1.76 g, 85%).
ν_{max}(film)/cm^{-1} 1778, 1740 (C=O), 1525 (C=C Ar). δ_H(400 MHz; $CDCl_3$) 6.14 (2H, s, OCH_2O), 7.42 (2H, d, *J* 9.2, *p*-NO_2Ar*H*), 7.49 (2H, t, *J* 8.0, Ar*H*), 7.64 (1H, t, *J* 7.6, Ar*H*), 8.12 (2H, d, *J* 7.2, Ar*H*) 8.29 (2H, d, *J* 9.2, *p*-NO_2Ar*H*).

[0045] The invention will now be further described with reference to the following Examples.

Example 1

(S)-3-(Benzoylaminomethyl)-5-methylhexanoic acid (4)

[0046] Benzoyl chloride (0.88ml, 7.6mmol) was added to a stirred suspension of pregabalin (1.0g, 6.3mmol) in THF (80 ml) at room temperature under argon and the reaction mixture was stirred for 18 hours. The reaction mixture was then filtered and concentrated *in vacuo*. The residue was chromatographed (SiO_2, heptane-ethyl acetate, 1:1 to 3:7) to give **4** (0.78 g, 47 %).

ν_{max}(film)/cm^{-1} 1705, 1634 (C=O), 1547 (C=C, Ar).
δ_H(400 MHz; $CDCl_3$) 0.92 (3H, d, *J* 6.8, C*H*$_3$), 0.94 (3H, d, *J* 7.6, C*H*$_3$), 1.20-1.30 (2H, m, C*H*$_2$CH(CH$_3$)$_2$), 1.69-1.79 (1H, m, C*H*(CH$_3$)$_2$), 2.20-2.30 (1H, m, C*H*CH$_2$CH(CH$_3$)$_2$), 2.35 (1H, dd, *J* 8.1, 14.7, CH_AH$_B$COOH), 2.45 (1H, dd, *J* 14.7, 4.2, CH$_A$*H*$_B$COOH), 3.38-3.43 (1H, m, CH_AH$_B$NH), 3.57-3.63 (1H, m, CH$_A$*H*$_B$NH), 6.63 (1H, bs, N*H*), 7.41-7.57 (3H, m, Ar*H*), 7.78 (2H, d, *J* 7.6, Ar*H*).

Example 2

(S)-Benzyl 3-(benzoylaminomethyl)-5-methylhexanoate (5)

[0047] Benzyl alcohol (0.31g, 3.0mmol) was added to a stirred mixture of (S)-3-(benzoylaminomethyl)-5-methylhexanoic acid **4** (0.78g, 3.0mmol), 1,3-dicyclohexylcarbodiimide (0.61g, 3.0mmol), and 4-dimethylaminopyridine (0.36g, 3.0mmol) in dichloromethane (40ml) and the mixture was stirred for 18 hours. The reaction mixture was, filtered and concentrated *in vacuo*. The residue was chromatographed (SiO_2, heptane-ether, 1:0 to 75:25) to give **5** (0.83 g, 79%).

ν_{max}(film)/cm^{-1} 1732, 1640 (C=O).

δ_H(400 MHz; $CDCl_3$) 0.89 (3H, d, *J* 7.2, C*H*$_3$), 0.91 (3H, d, *J* 6.8, C*H*$_3$), 1.19-1.30 (2H, m, C*H*$_2$CH(CH$_3$)$_2$), 1.64-1.75 (1H, m, C*H*(CH$_3$)$_2$) 2.23-2.35 (1H, m, C*H*CH$_2$CH(CH$_3$)$_2$), 2.39 (1H, dd, *J* 15.4, 7.3 , CH_AH$_B$COOH), 2.47 (1H, dd, *J* 15.4, 4.9, CH$_A$*H*$_B$COOH), 3.34-3.39 (1H, m, CH_AH$_B$NH), 3.52-3.58 (1H, m, CH$_A$*H*$_B$NH), 5.08 (2H, s, ArC*H*$_2$O), 6.64 (1H, bt, N*H*), 7.27-7.38 (5H, m, Ar*H*), 7.39-7.50 (3H, m, Ar*H*), 7.75 (2H, d, *J* 7.2, Ar*H*).

Example 3

(S)-3-[*N*-(acetoxymethyleneoxycarbonyl)aminomethyl]-5-methylhexanoic acid (6)

[0048] The carbonate **1** (1.0g, 3.9mmol) and pregabalin (0.62g, 3.9mmol) were stirred in THF (60ml) at room temperature for 48 hours. The reaction mixture was taken up in ethyl acetate (250 ml) and washed with water (200 ml), 1N HCl (200 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, heptane, then heptane-ethyl acetate, 1:1) to give **(6)** (0.18 g, 17%).

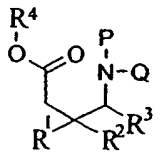
ν_{max}(film)/cm^{-1} 1715 (C=O).

δ_H(400 MHz; $CDCl_3$) 0.91 (3H, d, *J* 6.8, C*H*$_3$), 0.91 (3H, d, *J* 6.8, C*H*$_3$), 1.10-1.30 (2H, m, C*H*$_2$CH(CH$_3$)$_2$), 1.60-1.71 (1H, m, C*H*(CH$_3$)$_2$), 2.12 (3H, s, COC*H*$_3$), 2.15-2.35 (1H, m, C*H*CH$_2$CH(CH$_3$)$_2$), 2.27 (1H, dd, *J* 15.0, 8.0, CH_AH$_B$COOH), 2.37 (1H, dd, *J* 14.8, 4.4, CH$_A$*H*$_B$COOH), 3.10-3.17 (1H, m, C*H*HNH), 3.30-3.36 (1H, m, CH*H*NH), 5.28 (1H, bs, N*H*), 5.71 & 5.75 (OC*H*$_2$O).

[0049] From reagents **2** and **3** there may correspondingly be prepared (S)-3-[*N*-((2,2-dimethylpropionyloxymethyl-enoxy)carbonyl)aminomethyl)-5-methylhexanoic acid and (S)-3-[*N*-(benzoyloxymethyleneoxycarbonyl)aminomethyl]-5-methylhexanoic acid.

Claims

1. A compound of the formula (III)

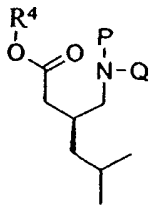


(III)

in which:

P is hydrogen or methyl;
Q is a labile amine- or amide-forming organic group that becomes removed in the human or animal body;
R^1 is straight or branched C_2 - C_6 alkyl, C_3 - C_6 cycloalkyl or phenyl;
R^2 is hydrogen or methyl; and
R^3 is hydrogen, methyl or carboxyl; and
R^4 is hydrogen or a labile ester-forming group selected from substituted and unsubstituted C_1 - C_6 alkyl, benzyl and phenyl groups that become removed in the human or animal body,
or a pharmaceutically acceptable salt of any salt-forming compound within the above class,
but excluding compounds in which R_1 is phenyl and R^2, R^3 and R^4 are each hydrogen.

2. A compound of the formula (IV)



(IV)

in which P, Q and R^4 have the meanings given in claim 1, and a pharmaceutically acceptable salt of any salt-forming compound within the above class.

3. The compound of claim 1 or 2, in which R^4 is hydrogen.

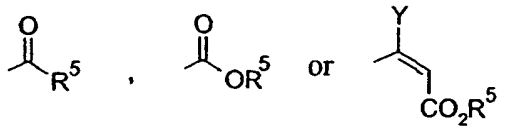
4. The compound of claim 1 or 2, in which R^4 is other than hydrogen and is more labile than Q.

5. The compound of claim 4, in which R^4 is methyl or *t*-butyl.

6. The compound of any preceding claim, wherein Q can be removed hydrolytically under physiological conditions.

7. The compound of any of claims 1-5, wherein Q can be removed enzymatically under physiological conditions.

8. The compound of any of claims 1-5, wherein Q is

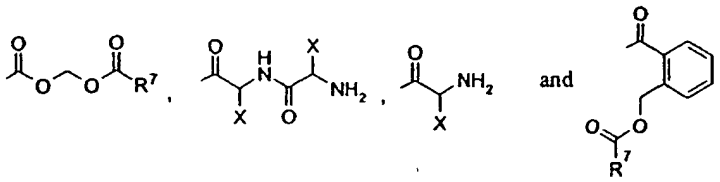


in which:

R^5 is hydrogen, straight or branched chain C_1 - C_6 alkyl, phenyl or benzyl in which the benzene ring may be substituted or unsubstituted; and
Y is hydrogen, straight or branched chain C_1 - C_6 alkyl, or $-CH_2CO_2R^6$ in which R^6 represents straight or branched chain C_1 - C_6 alkyl.

9. The compound of claim 8, wherein R^5 represents t-butyl, benzyl or phenyl.

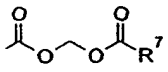
10. The compound of any of claims 1-7, wherein Q is selected from



in which:

R^7 is hydrogen, straight or branched chain C_1 - C_6 alkyl, phenyl or benzyl in which either or each benzene ring may be substituted or unsubstituted; and
X represents a phenyl group or any of the side chains of the 20 naturally encoded α-amino acids.

11. The compound of any of claims 1 - 7, wherein Q is

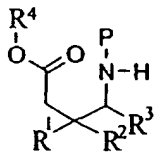


wherein R^7 is methyl, *t*-butyl or phenyl.

12. A compound selected from

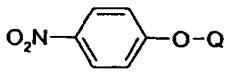
(S)-3-(Benzoylaminomethyl)-5-methylhexanoic acid;
(S)-Benzyl 3-(acylaminomethyl)-5-methylhexanoate;
(S)-3-[*N*-(acetoxymethyleneoxycarbonyl)aminomethyl]-5-methylhexanoic acid;
(S)-3-[*N*-((2,2-dimethylpropionyloxy)methyleneoxycarbonyl)-aminomethyl]-5-methylhexanoic acid;
(S)-3-[*N*-(benzoyloxymethyleneoxycarbonyl)aminomethyl)-5-methylhexanoic acid; and
pharmaceutically acceptable salts of any of the above.

13. A method for making a compound of the formula (III) or salt thereof, as defined in claim 1, above, which comprises:
coupling a compound of the formula:



(V)

in which P and R^1 - R^4 have the meanings given in claim 1 and in which said compound is in the form of a free base or an ammonium salt with a compound of the formula



or QCl where Q has the meaning given in claim 1.

14. The method of claim 13, in which the compound (V) is a carboxylic acid and comprising the further step of esterifying the carboxyl group with a substituted or unsubstituted C_1 - C_6 alkanol, benzyl alcohol or phenol.

15. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-12 and a pharmaceutically acceptable carrier.

16. A method for treating epilepsy comprising administering a therapeutically effective amount of a compound according to any of claims 1-12 to a human or animal in need of said treatment.

17. A method for treating faintness attacks, hypokinesia and cranial disorders comprising administering a therapeutically effective amount of a compound according to any of claims 1-12 to a human or animal in need of said treatment.

18. A method for treating a neurodegenerative disorder comprising administering a therapeutically effective amount of a compound according to any of claims 1-12 to a human or animal in need of said treatment.

19. A method for treating depression comprising administering a therapeutically effective amount of a compound according to any of claims 1-12 to a human or animal in need of said treatment.

20. A method for treating anxiety comprising administering a therapeutically effective amount of a compound according to any of claims 1-12 to a human or animal in need of said treatment.

21. A method for treating panic comprising administering a therapeutically effective amount of a compound according to any of claims 1-12 to a human or animal in need of said treatment.

22. A method for treating pain comprising administering a therapeutically effective amount of a compound according to any of claims 1-12 to a human or animal in need of said treatment.

23. A method for treating a neuropathological disorder comprising administering a therapeutically effective amount of a compound according to any of claims 1-12 to a human or animal in need of said treatment.

24. A method for treating a digestive disorder comprising administering a therapeutically effective amount of a compound according to any of claims 1-12 to a human or animal in need of said treatment.

25. Use of a compound according to any of claims 1-12 in the manufacture of a medicament for the treatment of any of the following:

epilepsy; hypokinesia; a neurodegenerative disorder; anxiety; pain; a digestive disorder.	a faintness attack; a cranial disorder; depression; panic; a neuropathological disorder

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 01 30 6484

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	MEINRAD BRENNER ET AL.: "Enantioselective preparation of gamma-amino acids..." HELVETICA CHIMICA ACTA., vol. 82, 1999, pages 2365-2379, XP001024955 VERLAG HELVETICA CHIMICA ACTA. BASEL., CH ISSN: 0018-019X * page 2369; page 2376, last paragraph; page 2367 *	1-8	C07C233/83 C07C271/22 A61K31/195 A61P25/00 A61P25/08
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INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
BERLIN	9 October 2001	Rufet, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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INCOMPLETE SEARCH
SHEET C

Application Number
EP 01 30 6484

Although claims 16-24 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) searched completely:
8-14

Claim(s) searched incompletely:
1-7,15

Reason for the limitation of the search:

Present claims 1-7 and 15 relate to products or pharmaceutical compositions thereof defined by reference to a desirable characteristic or property, namely having a labile bonding group which can be removed in the human or animal body.

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC and/or disclosure within the meaning of Article 83 EPC for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 84 EPC). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products according to formula (III) of claim 1 wherein Q has the definition given by claim 8.

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Application Number
EP 01 30 6484

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X	T. K. BURIMOVA ET AL.: "Preparation of dipeptides of gamma-aminocarboxylic acids" J. ORG. CHEM. USSR (ENGL. TRANSL.), vol. 8, 1972, pages 541-543, XP000926649 * the whole document * ---	1,4-8	
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EPO FORM 1503 03.82 (P04C10)

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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 01 30 6484

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X	CHEMICAL ABSTRACTS, vol. 131, no. 6, 9 August 1999 (1999-08-09) Columbus, Ohio, US; abstract no. 67642c, GUILLON, JEAN ET AL.: "Pharmacological evaluation of new baclofen derivatives" page 21; column 1; XP002179592 * abstract * & PHARM. PHARMACOL. COMMUN., vol. 5, no. 3, 1999, pages 243-247,	1,3,8, 15,25	TECHNICAL FIELDS SEARCHED (Int.Cl.7)

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 30 6484

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09-10-2001

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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